REMARKS

I. Introduction

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 1-27, 30-32, 42-46, and 52-53 are requested to be cancelled. The cancellation of claims does not constitute acquiescence in the propriety of any rejection set forth by the Examiner. Applicants reserve the right to pursue the subject matter of the canceled claims in subsequent divisional applications.

Claims 28, 37, 41, 47, 50-51, and 54 are currently amended.

Claim 55 is new.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claims remain under examination in the application, is presented, with an appropriate defined status identifier.

Upon entry of this Amendment, claims 28-29, 33-41, 47-51, and 54-55 will remain pending in the application.

Because the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested.

II. Response to Issues Raised by Examiner in Outstanding Office Action

a. Claim Rejections - 35 U.S.C. § 112, First Paragraph

Claims 28-29, 33-41, and 47-54 are rejected by the Examiner under 35 U.S.C. § 112, first paragraph for lack of enablement. Applicants respectfully request reconsideration and withdrawal of the rejection.

The Examiner asserts that while the specification is enabling for the disclosed full length sequences SEQ ID Nos. 6, 7, 8, and 9 the specification is not enabling for the

corresponding fragments. Applicants disagree with the Examiner's assertion, but, in order to facilitate prosecution, have amended the above claims to now recite full length SEQ ID NO. 9. In light of the these amendments, Applicants respectfully request reconsideration and withdrawal of the rejection.

b. Claim Rejections - 35 U.S.C. § 112, Second Paragraph

Claims 28-29, 33-41, and 47-54 are rejected by the Examiner under 35 U.S.C. § 112, second paragraph as being allegedly indefinite. Applicants respectfully request reconsideration and withdrawal of the rejection.

The Examiner asserts that Claim 28 is indefinite for not indicating if the method requires fluorescence or radiolabeled materials. See Office Action, p. 4. Applicants believe a reading of the entire specification provides extensive description of many methods for detection. See, for example, page 23, last paragraph, of the specification, and methods throughout the Examples. These sections describe detection means such as electron microscopy, circular dichroism spectroscopy (also see Example III and corresponding figures), fluorescence spectroscopy (also see Example XIII and corresponding figures), and infrared spectroscopy. In addition, page 16 describes additional assays such as agglutination assays, and immuno assays, for example, ELISAs, RIAs, IRMAs, FIAs, CLIAs, or ECLs. A reading of the entire specification should not be restrict claim 28 to require fluorescence or radiolabeled materials.

The Examiner asserts Claims 28 and 29 are indefinite for the recital of the term "fragments." See Office Action, p. 4-5. As noted above, Applicants have amended the claims to remove the term "fragment."

The Examiner asserts Claim 33 is unclear because it does not recite which steps are needed to synthesize the inhibitor, i.e. organic synthesis or polypeptide synthesis. See Office Action, p. 5. Applicants believe a reading of the entire specification provides extensive description of many methods for synthesis. See, for example, page 9-11, of the specification. These portions as well as others describe methods including organic synthesis and

polypeptide synthesis. Other methods are also disclosed in the specification and would be clear a person of ordinary skill in the art reading the specification.

The Examiner asserts that Claim 41 is unclear due to the term "optionally." See Office Action, p. 5. Applicants have amended the claims to remove the term "optionally."

The Examiner asserts that Claim 41 is unclear because of the term "suitable means of detection." See Office Action, p. 5. Applicants believe a reading of the entire specification provides extensive description of many methods for detection. See, for example, page 23, last paragraph, of the specification, and methods throughout the Examples. These sections describe detection means such as electron microscopy, circular dichroism spectroscopy (also see Example III and corresponding figures), fluorescence spectroscopy (also see Example XIII and corresponding figures), and infrared spectroscopy. In addition, page 16 describes additional assays such as agglutination assays, and immuno assays, for example, ELISAs, RIAs, IRMAs, FIAs, CLIAs, or ECLs. This extensive disclosure sufficiently describes to one of skill in the art how detection may be accomplished.

In light of the proceeding amendments and arguments, Applicants respectfully request reconsideration and withdrawal of this rejection.

c. Claim Rejections - 35 U.S.C. § 102

Claims 28-29, 33-41, 49-51, and 54 are rejected by the Examiner under 35 U.S.C. § 102 as being anticipated by Wischik, et al. (WO 96/30766) Applicants respectfully request reconsideration and withdrawal of the rejection.

WO 96/30766 discloses a specific method of screening for modulators of tau-tau association whereby a tau protein comprising a "tau core fragment" is screened in combination with "labeled tau protein or a labeled derivative thereof" as stipulated in claim 1a and lc of WO 96/30766. The "core fragment" of tau terminates, in accordance with claim 11 of WO 96/30766, with an alanine at position 390.

On page 11, line 6 to 25, WO 96/30766 defines the "tau core fragment" as being derived from the tandem repeat region and teaches an amino acid sequence which is at least

70% identical to the human tau protein amino sequence as shown in SEQ ID NO. 5 or in Figure 21. As a tau-core sequence, the fragment as shown in Figure 22 or the sequences as depicted in Figures 25 and 26 (SEQ ID NOs. 9 and 10 of WO 96/30766 are described. Figure 22 of WO 96/30766 comprises more than 90 amino acid residues, whereby SEQ ID NO. 25 or 26 comprise more than 100 amino acid residues. The "minimal protease-resistant PHF-tau unit" is taught in WO 96/30766 to comprise the "equivalent of 3 repeats", i.e. 93/95 residues; see page 32, lines 6 to 8.

In contrast, the present invention provides for very specific "minimal peptides" as identified, in particular the peptides shown in SEQ ID NOs. 7-9. This specific peptide is shown for the first time and surprisingly as comprising an intrinsic β-sheet propensity which is the distinct "nucleation site for PHF assembly"; see also, inter alia, application as filed page 7, second full paragraph to page 8, first paragraph as well as page 11 second paragraph of the application as filed. Also the application clearly documents that only fragments comprising the minimal VQIVYK motif as depicted in SEQ ID NO. 7-9 are capable of specific aggregation and/or of providing the minimal nucleation site for PHF formation.

Nowhere in WO 96/30766 is disclosed that such a short peptide sequence has a high intrinsic β-sheet propensity and is, accordingly responsible for PHF formation per se.

In this context, it is of note that WO 96/30766 merely describes an assay for the association (of) tau to tau; see example 1. In said assay ("tau-tau binding assay") the binding from tau to tau (indiscriminating whether this is a specific binding or an unspecific association) is measured in the ELISA assay employing an antibody directed against tau. This is in stark contrast to the present invention, where for the first time a paired-helical filament formation can be measured. Only the method of the present invention, employing the specific minimal peptides as characterized in SEQ ID NOS: 6 to 9, provides for means for specifically detecting paired helical filament nucleation formation and/or aggregation. In contrast to WO 96/30766 the present invention provides for means and methods where thin or short filaments/filament formation can be measured, inter alia, by spectroscopic methods and/or the specific detection of β-helical structures.

Accordingly, WO 96/30766 merely defines a rather long tau fragment which appears to be involved in tau interaction. The specific sequences consisting of tau derived peptides as shown in SEQ ID NOs. 6, 7, 8 or 9 are neither disclosed nor proposed in WO 96/30766. Furthermore, WO 96/30766 does not teach that the preparation as defined in the present application is capable of a fast β-sheet conformation transition. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

d. Claim Rejections - 35 U.S.C. § 103

Claims 47-48 are rejected by the Examiner under 35 U.S.C. § 103 as being obvious over Wischik et al. (WO 96/30766) in view of Vandermeeren et al.. Applicants respectfully request reconsideration and withdrawal of the rejection.

The Examiner asserts, "Wischik et al. do not explicitly teach using a kit to conduct the assay for screening potential candidates of PHF inhibitors. Vandermeeren et al. teach using a standard kit containing protein recognizing PHF-tau region as a convenient and economical tool for detecting neurological diseases." See Office Action, p. 7.

To establish a *prima facie* case of obviousness, there needs to be (1) some suggestion or motivation to modify the reference or to combine reference teachings, (2) a reasonable expectation of success, and (3) the prior art references, when combined, must teach or suggest all the limitations of the claimed invention. *See* MPEP §2143 (Aug. 2001). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). Applicants respectfully assert that the examiner has not met his burden.

As noted above, Applicant believes WO 96/30766 does not anticipate the present claims pertaining to SEQ ID NO. 9 and therefore, can not teach all of the limitations of the claimed invention. In addition, Vandermeeren concerns antibodies for diagnosing Alzheimer's disease which are directed to the sequence of Tau relating to amino acids 143 to 254. The present application, however, is neither concerned with phosphorylation dependent antibodies nor with that portion of tau. Rather, the present invention relates to another part of the sequence and its relevance for the aggregation of tau. Based on these distinctions, one

would not be motivated to combine the teachings of Vandermeeren with WO 96/30766. In light of the above, Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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